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Correlation of serum fibroblast growth factor-23 levels and calcium phosphate products levels in chronic kidney disease; sub analysis of chronic kidney disease-mineral and bone disorder study

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ABSTRACT

Introduction: The body produces fibroblast growth factor-23 (FGF-23) to maintain normal phosphate levels when hyperphosphatemia occurs. Production of FGF-23 indirectly causes hypocalcemia. Phosphate and calcium disturbances also occur in chronic kidney disease (CKD), therefore this adaptation mechanism applies. This situation; however, only manifests in the early stages of CKD; if the estimated glomerular filtration rate (eGFR) is less than 30% of normal. This adaptation is no longer adequate and levels of calcium-phosphate (Ca×P) products and FGF-23 still rise.

Objectives: In this study, the correlation between both the serum levels of FGF-23 and Ca×P products in CKD was analyzed.

Patients and Methods: A cross-sectional study including 78 subjects with CKD stages 3 to 5 dialysis was conducted. Serum FGF-23 levels were determined using the enzyme-linked immunosorbent assay (ELISA) method and Ca×P product levels were calculated using the formula calcium (mg/dL) × phosphate (mg/dL). The Kolmogorov-Smirnov test and Spearman's test were conducted in the statistical study. If the P value is less than 0.05, the statistical findings are significant.

Results: Serum FGF-23 levels and Ca×P product levels were shown to be significantly correlated. This analysis of the two correlations was independent of age and diabetes mellitus (DM). Based on stages of CKD, serum FGF-23 levels and Ca×P product levels were discovered to be significantly correlated only at stage 5 of non-dialysis.

Conclusion: Increasing serum FGF-23 levels were correlated with increased Ca×P product levels, particularly in CKD stage 5 non-dialysis subjects. This correlation was independent of age and DM.

Original Article

Implication for health policy/practice/research/medical education:
In chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) of less than 30% of normal, serum fibroblast growth factor-23 (FGF-23) levels can rise together with Ca×P product values. According to our research, serum FGF-23 levels and calcium-phosphate (Ca×P) products levels were correlated, particularly in CKD stage 5 non-dialysis. It can be a benchmark for determining how CKD is progressing and diagnosing chronic kidney disease-mineral and bone disorder (CKD-MBD) by examining FGF-23, calcium and phosphate levels.

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Introduction

A three-month-old kidney disorder condition that affects the structure and/or function of the kidneys and has negative health effects is known as chronic kidney disease (CKD) (1). One of the manifestations of CKD is a disturbance in the homeostasis of minerals, particularly phosphate and calcium. The hormone that is most frequently linked to CKD and acts to regulate the body's phosphate levels is fibroblast growth factor-23 (FGF-23) (2). When hyperphosphatemia occurs, FGF-23's major

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effects are to increase phosphate excretion through the urine and reduce phosphate reabsorption in the renal tubules by reducing the expression of NaPi-IIa and NaPi-IIc co-transporters. FGF-23 also decreased the expression of NaPi-IIb co-transporter, calcitriol levels and 1-alpha hydroxylase in the kidney, which inhibited the absorption of phosphate in the small intestine and kept phosphate levels within a consistent normal range (3). This compensatory mechanism is no longer adequate to maintain equilibrium in CKD with the estimated glomerular filtration rate (eGFR) at 30% of normal, leading to hyperphosphatemia. There is reduced calcitriol, which not only controls phosphate levels, but also prevents calcium from being absorbed in the small intestine, leading to hypocalcemia. Hypocalcemia further stimulates the prolonged secretion of parathyroid hormone (PTH). An increase in PTH accelerates the loss of calcium from bone, which is followed by a progressive accumulation of calcium and phosphate in tissues, causing vascular calcification (4-6). The calcium-phosphate (Ca×P) products is an indicator that describes calcium and phosphate metabolism (7). The disruption of Ca×P product homeostasis will cause alterations in the histological structure and bone strength, referred to as the mineral and bone disorders in CKD (8). Accordingly, Ca×P product homeostasis is maintained by endogenous factors such as age (9,10). Insulin resistance and insulin deficiency have been identified as the factors that stimulate FGF-23 production (11). Moreover, serum FGF-23 levels and Ca×P products that are associated with decreasing the eGFR. Therefore, we examined the relationship between serum FGF-23 levels and Ca×P product levels in this study.

Objectives

In this study, it was decided to find out the correlation between both serum FGF-23 levels and Ca×P product levels in patients with CKD stages 3 to 5 on dialysis and to investigate the effects of age and DM on that correlation.

Patients and Methods

Study design

This cross-sectional study was conducted at the Wahidin Sudirohusodo hospital in Makassar, South Sulawesi, Indonesia. The study took place from April to August 2021. The inclusion criteria of this study were CKD patients aged 18 to 65 years, with categories being stages of 3, 4, 5 non-dialysis and 5 on dialysis of ≥6 months. The distribution of CKD stage 3 (n = 19), stage 4 (n = 19), stage 5 non-dialysis (n = 20) and stage 5 dialysis (n = 20) included 78 subjects in the samples. Examination of serum FGF-23 levels was measured using a special research reagent kit using the method of the enzyme-linked immunosorbent assay (ELISA), (Immunotopics, Inc., Athens, made in the USA). The serum calcium level was measured using the arsenazo III method, using the Architect c8000 product. The serum phosphate level was measured by the phosphomolybdate method, using an architect c8000 product. Then the Ca×P product level was obtained with the formula calcium (mg/dL) × phosphate (mg/dL).

Statistical analysis

Statistical tests were performed on the data using SPSS version 25, which comprised frequency distribution and calculations for descriptive statistics. The types of statistical tests used were the Kolmogorov-Smirnov test to assess the normality of the data and Spearman's correlation test to assess the correlation of the variables. If the value was $P<0.05$, the outcomes of statistical tests were considered significant.

Results

There was not a discernible correlation between the levels of serum calcium and FGF-23 ($P=0.989$, r = 0.002). The levels of serum FGF-23; however, were significantly correlated with those of phosphate ($P=0.001$, r = 0.383). In a similar way, a substantial correlation between the serum levels of FGF-23 and Ca×P products was found ($P=0.000$, r = 0.419), with the higher the serum FGF-23 level, the higher the Ca×P product level (Tables 1 and 2).

Based on the stages of CKD in this study, the levels of serum calcium and FGF-23 did not significantly correlate with one another at all stages ($P>0.05$). Furthermore, a significant correlation between serum FGF-23 levels and serum phosphate levels was found at stage 3 and stage 5 non-dialysis ($P<0.05$). Meanwhile, serum FGF-23 levels

Table 1. Baseline characteristics of subjects

Variable	Minimum	Maximum	Mean	Standard deviation
Age (y)	18	65	48.50	12.54
eGFR (mL/min/1.73m^2)	1.10	56.30	20.98	16.69
Calcium (mg/dL)	5.40	11.40	8.11	1.05
Phosphate (mg/dL)	1.50	15.00	4.98	2.50
Ca×P product (mg^2/dL^2)	15.30	120.00	39.60	18.49
FGF-23 (RU/mL)	12.30	2013.20	387.9	423.50

Variable descriptive statistics (n=78).
Abbreviations: eGFR, estimated glomerular filtration rate; Ca×P, Calcium phosphate; FGF-23, fibroblast growth factor-23.

Table 2. FGF-23 with calcium, phosphate and Ca×P products of correlated

Variable	Statistics	Calcium	Phosphate	Ca×P product
FGF-23	r	0.002	0.383	0.419
	P	0.989	**0.001**	**0.000**
	n	78	78	78

Spearman's rho test.
Abbreviations: Ca×P, Calcium phosphate; FGF-23, fibroblast growth factor-23.

and Ca×P product levels were only significantly correlated at stage 5 non-dialysis ($P < 0.001$, r = 0.722; Table 3).

The effect of age analysis was still found to have a significant correlation between serum FGF-23 levels and Ca×P product levels on the age factor as age <60 years ($P = 0.001$, r = 0.405) and age ≥60 years ($P = 0.030$, r = 0.541). Therefore, the age factor was independent of the correlation between serum FGF-23 levels and Ca×P product levels in CKD. Subjects with DM ($P = 0.013$, r = 0.449) and subjects without DM ($P = 0.009$, r = 0.373) had significantly correlated serum FGF-23 levels and Ca×P product levels on these variables. Consequently, whether or not there was DM, there was an independent correlation between serum levels of FGF-23 levels and Ca×P products (Table 4).

Discussion

In this study, the correlation study showed serum calcium and FGF-23 levels, with no statistically significant link ($P = 0.989$, r = 0.002). A significant correlation between serum phosphate levels and serum FGF-23 levels was discovered through research work ($P = 0.001$, r = 0.383). Analysis of the correlation of serum FGF-23 levels with Ca×P product levels also found a significant correlation ($P = 0.000$, r = 0.419). These findings were in line with the study by Yasin et al (2) in 2013, a cross-sectional investigation of 81 patients identified a strong association between FGF-23 and Ca×P products in CKD patients older than 13 years old with stages 1 to 5 of the condition ($P < 0.0001$, r = 0.534).

Based on an analysis of CKD stages, no significant

Table 3. Based on the stages of CKD in correlated FGF-23 with calcium, phosphate and Ca×P products

CKD	Variable	Statistics	Calcium	Phosphate	Ca×P product
Stage 3	FGF-23	r	-0.252	0.539	0.358
		P	0.299	0.017	0.132
		n	19	19	19
Stage 4	FGF-23	r	0.136	0.200	0.249
		P	0.578	0.413	0.304
		n	19	19	19
Stage 5 non-dialysis	FGF-23	r	0.055	0.715	0.722
		P	0.819	<0.001	<0.001
		n	20	20	20
Stage 5 on dialysis	FGF-23	r	0.208	-0.118	-0.057
(≥6 months)		*P*	0.378	0.620	0.811
		n	20	20	20

Spearman's rho test.
Abbreviations: CKD, chronic kidney disease; Ca×P, Calcium-phosphate; FGF-23, fibroblast growth factor-23.

Table 4. The characteristics and effects of other factors on the correlation of FGF-23 with Ca×P product

Factors	Variable	Statistics	Ca×P product	N	%
Ages					
<60 years	FGF-23	r	0.405	62	79.5
		P	**0.001**		
≥60 years	FGF-23	r	0.541	16	20.5
		P	**0.030**		
DM					
Yes	FGF-23	r	0.449	30	38.5
		P	**0.013**		
No	FGF-23	r	0.373	48	61.5
		P	**0.009**		
Total				78	100

Spearman's rho test.
Abbreviations: Ca×P, Calcium-phosphate; FGF-23, fibroblast growth factor-23.

correlation between serum FGF-23 levels and Ca×P levels at stages 3 and 4 was detected. This study was supported by the study of Isakova et al (12) that examined a cohort data. They found significant diversity across all phases of eGFR, since not all CKD patients had increased FGF-23 levels. This condition could be impacted by physiological or genetic factors. In CKD stage 5 non-dialysis, a significant correlation was found between FGF-23 levels and Ca×P product levels. This result was consistent with a study by Kritmetapak et al (13), involving 85 subjects with varied eGFR levels, which revealed a progressive rise in FGF-23 and Ca×P product concentration as eGFR decreased. Levels of serum FGF-23 and Ca×P products were not significantly correlated in subjects with CKD stage 5 who had been receiving dialysis for six months. Phosphate levels decreased with longer and more frequent dialysis sessions, but FGF-23 levels remained the same (14).

In terms of age and DM, there was still a significant correlation between serum FGF-23 levels and Ca×P product levels in CKD (Table 4). This shows that these factors were independent of the correlation between the two. We were aware of a few studies investigating the effect of age and DM on the correlation between levels of Ca×P products and serum FGF-23 in CKD.

Conclusion

Increasing serum FGF-23 levels were correlated with increased Ca×P product levels, particularly in CKD stage 5 non-dialysis subjects. The level of Ca×P product rises in direct proportion to the level of FGF-23 in the serum. This correlation was independent of age and DM.

Limitations of the study

This study did not investigate the history of diet, using calcitriol, phosphate binders, and calcium supplements, all of which can affect Ca×P product levels. An albumin examination was not performed to measure total calcium levels.

Authors' contribution

Conceptualization: Adeh Mahardika, Hasyim Kasim, Syakib Bakri.
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Conflicts of interest

The authors state that they have no interest in conflict.

Ethical issues

The Declaration of Helsinki was followed in the conduct of this study. This study was approved by the Human Biomedical Research Ethics Committee at the Faculty of Medicine of Hasanuddin University in Makassar, South Sulawesi, Indonesia with project ID: UH-21100641, and Reference No: 856/UN4.6.4.5.31/PP36/2021. Each subject gave their written informed consent. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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